

REMARKS

INTRODUCTORY MATTERS

Claims 6-9 are pending in this application. Claims 1-5 and 10-19 are withdrawn and claims 20 and 21 are canceled. Following entry of this amendment, claims 6-9 will be pending.

THE CLAIM AMENDMENTS

Applicants have amended claims 6-9 to recite a latent OP-1 fusion protein. Support for this amendment is provided throughout the specification.

None of the amendments introduces any new matter.

THE OBJECTIONS

The Specification

The Examiner has objected to the specification stating that the disclosure at page 79 contradicts the disclosure at page 77. Specifically, the Examiner states that at page 79, 2nd paragraph, the specification discloses that a modified morphogen containing a collagen binding domain (*e.g.*, H2487 shown in Figure 7A) can be delivered in an inactive form to a desired tissue locus and cleaved at that locus to produce an active morphogen, whereas the disclosure at page 77, lines 16-20 discloses that a fusion protein of H2487 comprising a collagen binding domain and modified OP-1 was successfully active in the ROS assay and that appropriate correction is required. Applicants traverse.

Applicants respectfully submit that the disclosures at pages 79 and 77 are not contradictory and no correction is necessary. The specification at page 79, first full paragraph, discloses that cleavage of a latent protein at a target locus may be the result of conditions

endogenous to the target locus such as naturally occurring proteases. The first full paragraph at page 79 also discloses that other factors such as acidic conditions are also capable of cleaving the latent protein. The disclosure at page 76 does not contradict this. The fact that H2487 is active in the ROS assay does not necessarily mean that the intact construct itself is active. Rather, the culture conditions used with the ROS assay may contain a protease or other factors and conditions (*e.g.*, acidic conditions) which cleave the H2487 construct, thereby releasing the active form of the morphogen. This is consistent with the disclosure at page 79 that local conditions at a target locus, such as proteases or acidic conditions can result in cleavage of the latent protein. Accordingly, applicants request that the Examiner withdraw this objection.

THE REJECTIONS

35 U.S.C. § 112, First Paragraph

The Enablement Rejection

The Examiner has rejected claims 6-9, 20 and 21 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner states that the specification, while being enabling for the latent fusion proteins, H2440 and H2487, is not enabling for the skilled worker to make and/or use the invention commensurate in scope with the claims. Specifically, the Examiner states that the claims encompass a genus of cleavable leader sequences operably linked to a genus of TGF- β family protein C-terminal domains and that while the specification discloses numerous leader sequences that can be used to make a fusion protein, it fails to provide sufficient guidance and/or working examples with respect to how to make any other latent TGF- β family member fusion proteins such as a latent fusion protein comprising a first TGF- β family protein C-terminal domain and a leader sequence derived from a second TGF- β family protein, or a fusion TGF- β family protein wherein a part of the leader sequence is cleaved. The Examiner

further states that while the specification discloses that some N-terminal fusion protein monomers do not form active homodimers without cleavage of the leader sequence, the specification does not provide description of the structural feature that makes a leader sequence inhibit the biological activity associated with a TGF- β family protein C-terminal domain and thus renders a TGF- β family member fusion protein latent. The Examiner further states that whether a refolded TGF- β fusion is active or not depends not only upon the structure of the fusion protein such as the leader sequence, but also on the refolding conditions.

Applicants traverse. However, solely to expedite prosecution of this application, applicants have amended the claims to recite a latent OP-1 fusion protein. The specification describes how to make and use a latent OP-1 fusion protein as recited in the amended claims of the instant application. For example, the specification at page 77, lines 8-14 discloses a modified OP-1 protein, H2440, which is a properly refolded but inactive latent protein, and is subsequently cleaved to release an active OP-1. Applicants submit that this example provides the requisite enablement for the scope of the amended claims. Further, it would be unduly burdensome for applicants to have to exemplify each and every embodiment within the scope of the claims. For all the above reasons, applicants request that the Examiner withdraw the enablement rejection.

The Written Description Rejection

The Examiner has rejected claims 6-9, 20 and 21 under 35 U.S.C. § 112, first paragraph, for lack of written description. Specifically, the Examiner states that the claims encompass a genus of cleavable sequences operably linked to a genus of TGF- β family protein C-terminal domains. The Examiner states that the specification discloses 2 fusion proteins-- H2440 and H2487. The Examiner however, states that the disclosure relating to the activity of

H2487 in the ROS assay is contradictory. Accordingly, the Examiner concludes that the specification fails to disclose a representative number of species which would lead one skilled in the art to conclude that applicants were in possession of the claimed invention. The Examiner further states that the specification asserts that some N-terminal fusion protein monomers that do not form active homodimers without cleavage of the leader sequence form active heterodimers between those proteins and unmodified monomers of TGF- β family proteins. Therefore, the Examiner concludes that the latent TGF- β family member fusion proteins are really limited to the latent TGF- β family member fusion protein homodimers.

Applicants traverse. However, as discussed above, solely to expedite prosecution of this application, applicants have amended the claims to recite a latent OP-1 fusion protein comprising an OP-1 C-terminal seven cysteine domain and a cleavable leader sequence operably linked to said OP-1 C-terminal domain selected from the group consisting of a leader sequence derived from a TGF- β family protein other than OP-1, a metal-binding domain, a protein-binding domain, a ceramic-binding domain, a hydroxyapatite-binding domain and a collagen-binding domain. Applicants submit that the specification provides adequate written description for the claims as amended. The specification at, *e.g.*, page 19, lines 1-5, pages 37- 40 and Figure 5, provides written description for what is intended by OP-1 C-terminal domain. Further, the specification at, *e.g.*, pages 20-21 and 77-82 provides written description for the various cleavable leader sequences that are recited. Moreover, as discussed above, the disclosure with respect to the activity of H2487 in the ROS assay is not contradictory. Applicants have exemplified at least two latent OP-1 fusion protein -- H2440 and H2487. This is sufficient written description.

Applicants also note that the Examiner's conclusion that the latent TGF- β family member fusion proteins are limited to latent TGF- β family member fusion protein homodimers is unfounded. The specification at page 79 states:

Although some *N-terminal fusion protein monomers* as described above do not form active homodimers without cleavage of the leader sequence, active *heterodimers* are formed between *those proteins* and *unmodified monomers* of TGF- β family proteins.

The statement relating to heterodimers refers to dimeric proteins wherein only one of the two monomers is a fusion protein. The other is an unmodified monomer. This disclosure in no way implies that a heterodimer of two different TGF- β family member fusion proteins would not be a latent heterodimer.

For all the above reasons, applicants request that the Examiner withdraw the written description rejection.

35 U.S.C. § 102(b)

The Examiner has rejected claims 6-8 and 20 under 35 U.S.C. § 102(b) as being anticipated by Hall et al., WO 96/39430 ("Hall"). The Examiner contends that Hall teaches a TGF- β fusion protein comprising a TGF- β 1 active fragment and a leader sequence, which may comprise a purification tag, proteinase sensitive linker sites and a protein binding domain. The Examiner further states that Hall teaches that the refolded fusion protein under low concentrations of urea and DTT or a redox system using DTT in conjunction with glutathione had little biological activity. The Examiner concludes that since the fusion protein appears to satisfy the structural requirement, the additional properties recited in claims 6-8 are inherent to the structure of the fusion protein.

Applicants traverse. Applicants have amended the claims to recite a latent *OP-1* fusion protein. Hall discloses *TGF-β1* fusion proteins. Hall does not disclose OP-1 fusion proteins. Further, applicants note that Hall does not disclose that the renaturation of the fusion proteins under low concentrations of urea and DTT or a redox system using DTT in conjunction with glutathione resulted in a properly refolded protein. By contrast, the claims of the instant application recite that the latent protein is a *refolded protein*. Moreover, Hall discloses that the fusion protein renatured using the modified glutathione redox system (method III) did have biological activity (see page 14, lines 8-24) even when the leader sequence was present. By contrast, the claims of the instant application require that the cleavable leader sequence inhibit the biological activity of OP-1, and that the OP-1 does not become active until the leader sequence is cleaved. Accordingly, for all the above reasons, Hall does not anticipate the amended claims of the instant application.

35 U.S.C. § 102(e)

The Examiner has rejected claims 6-8, 20 and 21 under 35 U.S.C. § 102(e) as being anticipated by Nimni et al., U.S. Patent No. 6,352,972 ("Nimni"). The Examiner contends that Nimni¹ teaches a TGF-β fusion protein comprising a TGF-β1 active fragment and a leader sequence, which may comprise a purification tag, proteinase sensitive linker sites and a protein binding domain. The Examiner further states that Nimni teaches that the refolded fusion protein under low concentrations of urea and DTT or a redox system using DTT in conjunction with glutathione had little biological activity. The Examiner also states that Nimni teaches a fusion protein comprising the active portion of BMP proteins such as OP-1. The Examiner concludes

¹ Throughout the rejections set forth on page 12, the Examiner refers to Hall. However, applicants believe that the Examiner intended to refer to Nimni instead.

that since the fusion protein appears to satisfy the structural requirement, the additional properties recited in claims 6-8 are inherent to the structure of the fusion protein.

Applicants traverse. Applicants have amended the claims to recite a latent OP-1 fusion protein. Nimni discloses specific TGF- β 1 and BMP-3 fusion proteins. Although Nimni discloses OP-1 (BMP-7) as one of the TGF- β proteins that may be used, it does not disclose any specific examples of OP-1 fusion proteins.

Further, like Hall, Nimni also does not disclose that the renaturation of the TGF- β 1 fusion proteins under low concentrations of urea and DTT or a redox system using DTT in conjunction with glutathione resulted in properly refolded protein. By contrast the claims of the instant application recite that the latent protein is a *refolded protein*. Moreover, Nimni discloses that the TGF- β 1 fusion protein renatured using the modified glutathione redox system (method III) did have biological activity (see column 10, line 66 to column 11, line 22) even when the leader sequence was present. Similarly, the BMP-3 fusion protein of Nimni also had biological activity even in the presence of the leader sequence. By contrast the claims of the instant application require that the cleavable leader sequence inhibit the biological activity of OP-1, and that the OP-1 does not become active until the leader sequence is cleaved.

Accordingly, for all the above reasons, Nimni does not anticipate the amended claims of the instant application.

CONCLUSION

In view of the foregoing remarks and amendments, applicants request that the Examiner favorably reconsider this application and allow the amended claims pending therein.

Should the Examiner feel that a telephone conference with applicants' representatives would assist the Examiner, she is invited to telephone the undersigned at any time.

Respectfully submitted,

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